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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,838	WEDEL ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-17 and 25-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-17 and 25-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5-26-2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 26, 2009 has been entered.

Status of Claims

Claims 1-3, 7-17, and 25-44 are currently pending and under examination on the merits in the instant case.

Response to Arguments

Applicant's arguments with respect to claims 1-3, 7-17, and 25-39 filed with the RCE have been considered but are moot in view of the new ground(s) of rejection. See below.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 43 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recites a pouchitis treatment method "wherein the composition is administered less than once daily." First, it is unclear how a therapeutic composition can possibly be administered less than once. From a logical point of view, the minimal unit of dosing frequency should be "one" or "once" because the "administration" is counted by the number of actual activity of administering. Hence, the claimed administration step must be "zero" or "no administration" daily because there is no "half" number of administration. As such, the claim language is so vague and unclear that one of ordinary skill in the art would not be able to ascertain how many times the claimed composition is administered on a daily basis, thereby rendering the claim indefinite. For examination purpose, the "less than once daily" will be interpreted to mean "at least once daily" in view of the preceding claims such as claims 40-42.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 43 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new matter rejection.

The claim is a newly entered claim that recites a limitation that was not presented in the application as originally filed. Applicant has pointed out paragraph 0142 and Example 17 for new claim support. However, there does not appear to be a written description of the claim limitation "less than once daily" in the passages pointed out by applicant. Accordingly, the claim limitation is considered to introduce new matter which is not adequately described in the application as originally filed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 7-17, and 25-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gewritz et al. (*Current Opinion in Investigational Drugs,* 2001, citation of record) in view of Patel et al. (*European Journal of Gastroenterology & Hepatology,* 1995, 7:1037-1041, citation of record), Sachetto et al. (US 7,341,741 B1, citation of record), Yacyshyn et al. (*Ailmentary Pharmacology & Therapeutics,* 2002, 16:1761-1770), and Bennett et al. (US 6,096,722, citation of record).

The claims are drawn to a method of treating pouchitis in a patient comprising rectally administering a pharmaceutical composition known as ISIS 2302 (gapmer antisense oligonucleotide of SEQ ID NO:1), wherein the composition is formulated for rectal use, wherein ISIS 2302 is an antisense oligonucleotide targeted to ICAM-1 and is rectally administered at least once every 10 weeks, wherein the treatment reduces a PDAI score to 2, and wherein the method reduces at least one clinical symptom selected from stool frequency, rectal bleeding, abdominal cramps, fever and reduces the PDAI score to less than 7, wherein the composition comprises 240 mg of ISIS 2302, wherein the treatment last for at least one every 6 weeks, a month, a week, or a day and reduces the clinical symptoms for at least one month after cessation of the treatment.

Gewritz et al. teach that an anti-ICAM-1 antisense oligonucleotide molecule known as ISIS-2302 has been developed into a therapeutic molecule known as "alicoforsen", which has been tested for various inflammatory bowel disorders (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC). They teach that "ICAM-1 expression is elevated in chronic inflammatory disease states including IBD, so reduction of ICAM-1 expression by alicaforsen can reasonably be expected to be therapeutic for this disorder. Supporting this notion, other pharmacological approaches to the inhibition of ICAM-1 activity, including small molecule inhibitors and

antibodies, consistently reduce the severity of inflammation in animal models." See pages 1401-1402. They teach that alicoforsen in an enema formulation has been developed and the use of enema formulated alicoforsen is tested for clinical efficacy for UC treatment. Gewritz et al. do not teach that alicoforsen (ISIS-2302) in edema formulation can be used to treat pouchitis, which is an inflammatory bowel disorder.

Patel et al. teach that pouchitis, Crohn's disease, and ulcerative colitis are classified as chronic inflammatory bowel disease (IBD) characterized by clinical symptoms such as diarrhea, rectal bleeding, abdominal pain, fever, and endoscopic evidence of mucosal inflammation. They teach that some patients with ulcerative colitis have clinical pouchitis (classified as "active disease" restorative proctolectomy), which displays a combination of clinical symptoms of frequency of stools, fecal urgency, rectal bleeding, and mucosal inflammation. They teach that patients with pouchitis have a significantly high level of plasma ICAM-1. See page 1040, right column: "The present study suggests that sICAM-1 and sE-Selection levels are significantly increased during active inflammatory bowel disease and pouchitis compared with the levels in inactive disease". They further note that the expression profile of cytokines and adhesion molecules including ICAM-1 is similar between pouchitis and ulcerative colitis and suggests that pouchitis is a reactivation of immunological processes underlying ulcerative colitis. See page 1040, right column: "Similar expression of adhesion molecules and cytokine expression in pouchitis and active ulcerative colitis suggest that pouchitis might represent a reactivation of the immunological mechanisms that brought about ulcerative colitis." Furthermore, they suggest that ICAM-1, a cell adhesion molecule that reflects lymphocyte activation and leucocyte migration, could be a target for the control of inflammatory bowel disease. See the last sentence on page 1040.

Sachetto et al. teach a method of treating patients having chronic pouchitis characterized by endoscopic mucosal inflammation and other clinical symptoms for more than 4 weeks, wherein the patients display a PDAI score of at least 7 points, comprising rectally administering a therapeutic amount of hydroxypropylmethylcellulose in an enema formulation, wherein the method reduces the PDAI score (clinical score, endoscopy score, histology score) to 2 points or 1 or zero point. They teach that the pouchitis treatment method is also useful in treating patients having ulcerative colitis or Crohn's disease. See column 9, lines 1-4; column 10, lines 34-37; claims 1-19.

Yacyshyn et al. teach that doses of 300 mg or 350 mg of alicaforsen (ISIS 2302) are effective for treating Crohn's disease (CD) in human patients weighing more than 50 kg and with Crohn's disease activity index (CDAI) score of greater than 220 or a dose of 250 mg of alicaforsen (ISIS 2302) is effective for CD patients weighing 36-50 kg when alicaforsen is administered by infusions three times a week for 4 weeks. They teach that the administration of alicaforsen results in the cessation of clinical symptoms for at least one month. They demonstrate that evaluating and determining doses, administration frequency, and administration duration based on the pharmacokinentics of alicaforsen for a particularly intended disease for treatment are within the technical grasp of one of ordinary skill in the art.

Bennett et al. teach a method of making enema formulations of ISIS 2302 for rectal administration, wherein some pre-clinical studies have shown that ISIS 2302 given by enema demonstrated good tolerability and tissue uptake. See Examples 46 and 55. They teach that such formulations distribute ISIS 2302 to the targeted colonic tissue of animals, demonstrating the bioavailability of the oligonucleotide of ISIS 2302 in the targeted tissue. See Examples 47-48. They further teach that a pharmaceutical composition comprising ISIS 2302 can be formulated as

suppositories and enemas for rectal use. See column 18, lines 13-27. They further teach that ISIS 2302 has been evaluated up to Phase II trials for patients with Crohn's disease and ulcerative colitis, where in said ISIS 2302 has consistently demonstrated desired therapeutic efficacy. See Examples 51-55. See also claims 9-11 and 16-19, which are drawn to methods of treating a human having inflammatory bowel disease or ulcerative colitis, or Crohn's disease, comprising administering a therapeutic amount of ISIS 2302 by formulating said ISIS 2302 in a penetration enhancer. They further teach that ICAM-1 inhibitors are useful for treating various inflammatory disorders of the bowel in an animal, wherein such disorders include, for example, gastrointestinal diseases such as inflammatory bowel disease, ulcerative colitis, Crohn's disease, and other forms of regional enteritis. See column 3, lines 32-49; column 21, lines 54-65.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use alicaforsen (a pharmaceutical composition comprising a gapmer antisense oligonucleotide targeted to ICAM-1 and has the nucleotide sequence of SEQ ID NO:1 claimed in the instant case) in an enema formulation to rectally administer alicaforsen into a human patient having pouchitis.

One of ordinary skill in the art would have been motivated to do so in order to treat pouchitis in a human patient having pouchitis because of the following reasons provided by the teachings of the prior art cited hereinabove.

1) Clinical use of alicaforsen for treating inflammatory bowel diseases (IBD) having an increased expression level of ICAM-1 was expressly suggested to be "reasonably" expected to be therapeutically useful by Gewritz et al. as following on page 1401: "ICAM-1 expression is elevated in chronic inflammatory disease states including **IBD**, so reduction of ICAM-1 expression by **alicaforsen can reasonably be expected to be therapeutic for this disorder**."

(emphasis added). Hence, it was known in the art that alicaforsen can be "reasonably" used to treat a chronic inflammatory bowel disease that shows increased ICAM-1 expression level.

2) ICAM-1 expression level was known to be significantly high in patients with pouchitis and those with ulcerative colitis and therefore ICAM-1 was suggested to be a useful therapeutic target for treatment of pouchitis and ulcerative colitis by Patel et al. In fact, co-occurrence of ulcerative colitis and pouchitis, similar expression profile of inflammatory cytokines and adhesion molecules between ulcerative colitis and pouchitis, similar clinical symptoms shared by ulcerative colitis and pouchitis, and the fact that ulcerative colitis patients often have pouchitis and that pouchitis is a reactivation of immunological processes underlying ulcerative colitis and therefore the clinical symptoms of pouchitis mimic original symptoms of ulcerative colitis were all known in the art as taught by Patel et al. Hence, it was known in the art that patients with pouchitis, a chronic inflammatory bowel disease (IBD), have increased ICAM-1 expression level and that the clinical aspects (e.g., pathogenesis, symptoms) of pouchitis are tightly associated with those of ulcerative colitis.

3) The interchangeability of a treatment method based on rectal administration of a therapeutic amount of hydroxypropylmethylcellulose in an enema formulation for pouchitis treatment as claimed in claim 33 in the instant case and ulcerative colitis treatment was known in the art as taught by Sachetto et al. See claim 1: "A method for the treatment of inflammatory bowel disease (IBD) comprising contacting the diseased mucosa of the gastrointestinal tract with a therapeutic amount of...hydroxypropylmethylcellulose (HPMC) as the sole therapeutic agent." See claim 2: "The method according to claim 1, wherein the disease state is pouchitis." See claim 3: "The method according to claim 1, wherein the disease state is left sided ulcerative colitis." See claim 8: "The method according to claim 1 wherein said therapeutic agent is rectally

administered in the form of an rectally administrable pharmaceutical composition." See claim 19: "A liquid enema composition for the treatment of inflammatory bowel disease (IBD), said composition comprising hydroxypropylmethylcellulose (HPMC) as the sole therapeutic active agent in an amount effective to treat inflammatory bowel disease". Hence, it was known in the art to rectally administer a therapeutic agent in an enema formulation such as alicaforsen (note that the enema formulation of alicaforsen was clinically tested to be safe and efficacious; distributed to the targeted colonic tissue for treatment of ulcerative colitis; and consistently demonstrated desired therapeutic efficacy as taught by Gewirtz et al. and Bennet et al.) to a patient having an IBD such as pouchitis to treat the IBD. Further, enema formulation of hydroxypropylmethylcellulose for rectal administration for pouchitis treatment was an art-recognized pouchitis treatment method and the enema formulation of alicaforsen for rectal administration for pouchitis treatment, wherein the enema formulation further comprises a penetration enhancer (see Bennett et al.) was suggested in the art for the reasons stated above. Therefore, making a combination therapeutic composition in an enema formulation comprising alicaforsen and hydroxypropylmethylcellulose for pouchitis treatment would have been obvious at the time of filing. See *In re Kerkhoven* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980), wherein the court expressed the following: "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose…[T]he idea of combining them flows logically from their having been individually taught in the prior art."

4) Evaluating clinical efficacy of alicaforsen for human patients and determining optimal dosage, dosing schedule, and dosing frequency based on a disease activity score were known to be within, not beyond, the technical grasp of one of ordinary skill in the art at the time of filing

as evidenced by the teachings of Yacyshyn et al. For example, doses of 300 mg or 350 mg of alicaforsen (ISIS 2302) were determined to be effective for treating Crohn's disease (CD) in human patients weighing more than 50 kg and with Crohn's disease activity index (CDAI) score of greater than 220, and similarly, a dose of 250 mg of alicaforsen (ISIS 2302) was determined to be effective for CD patients weighing 36-50 kg when alicaforsen is administered by infusions three times a week for 4 weeks. Further, a Pouchitis disease activity index (PDAI) score (clinical score, endoscopy score, histology score) was known to be indicative of pouchitis treatment effect or disease progression such that a score of 7 or more indicates active pouchitis and effective treatment is able to reduce the PDAI score to 2 or 1 or zero point as taught by Sachetto et al. Hence, obtaining a suitable or optimal dosing schedule (e.g., frequency, duration) and a therapeutically effective dosage for the enema formulation of alicaforsen based on the pouchitis disease index score system of PDAI as claimed in the instant case would have been reasonably expected at the time of filing in view of the state of the art and guidelines disclosed by Yacyshyn et al. and Sachetto et al.

In view of the foregoing, the claimed method of treating pouchitis in a human having pouchitis by rectally administering a clinically tested enema formulation of alicaforsen in a therapeutically effective dosage sufficient to reduce a PDAI score to 2 or 1 or zero point would have been *prima facie* obvious at the time of filing.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 7-17, and 25-44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 4-9 of copending Application No. 11/720,745. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims and the reference claims are drawn to a rectal use (method) of ISIS 2302 for treatment of a disease, wherein the ISIS 2302 results in amelioration of stool frequency, rectal bleeding, and disease activity index. Although

the reference claims do not explicitly recite "pouchitis" as the disease to be treated, the specification of 11/720,745 discloses that pouchitis is one of the diseases encompassed within the treatment use/method claims and therefore lowering the PDAI score is also contemplated within the claimed use of ISIS 2302. See pages 7 and 10. Further, the specification of 11/720,745 teaches that the rectal use of ISIS 2302 further includes a penetration enhancer and hydroxypropylmethylcellulose. See page 7. The specification also teaches that the use of ISIS 2302 at 240 mg also results in the reduced clinical symptoms for at least 6 weeks. See page 18. Hence, the scope of the claimed invention and the reference claims overlaps with each other and the claims in the instant application and the copending application are obvious variants of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/Dana Shin/
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